PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference REP07147WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/02586	International filing date *(day/month/year)* 17.06.2003	Priority date *(day/month/year)* 17.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/395		
Applicant ARAKIS LTD. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.01.2004	01.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hornich, E Telephone No. +49 89 2399-8721

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02586

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-4	as originally filed

Claims, Numbers

1-10	as originally filed
11-13	received on 02.07.2004 with letter of 30.06.2004

Drawings, Sheets

1-4	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 11-13
	No:	Claims	1-5, 7-10
Inventive step (IS)	Yes:	Claims	6, 12
	No:	Claims	1-5, 7-11, 13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION V

1. *References*:

D1: BENHAMOU D (REPRINT): 'Nefopam and combined analgesics' ANNALES FRANCAISES D ANESTHESIE ET DE REANIMATION, (DEC 2002) SP. ISS. SI, PP. 9-14. PUBLISHER: EDITIONS SCIENTIFIQUES MEDICALES ELSEVIER, 23 RUE LINOIS, 75724 PARIS CEDEX 15, FRANCE. ISSN: 0750-7658. Hop Bicetre, Dept Anesthesie Reanimat, AP HP, 78 Ave Gen Leclerc, F-94270 Le Kremlin Bicetre, France (Reprint); Hop Bicetre, Dept Anesthesie Reanimat, AP HP, F-94270 Le Kremlin Bicetre, France.

D2: MIMOZ O ET AL: 'Analgesic efficacy and safety of nefopam vs. propacetamol following hepatic resection.' ANAESTHESIA. ENGLAND JUN 2001, vol. 56, no. 6, June 2001 (2001-06), pages 520-525, ISSN: 0003-2409.

D3: MOFFAT A C ET AL: 'Postoperative nefopam and diclofenac. Evaluation of their morphine-sparing effect after upper abdominal surgery' ANAESTHESIA 1990 UNITED KINGDOM, vol. 45, no. 4, 1990, pages 302-305, ISSN: 0003-2409.

D4: PILLANS P I ET AL: 'Adverse reactions associated with nefopam.' THE NEW ZEALAND MEDICAL JOURNAL. NEW ZEALAND 22 SEP 1995, vol. 108, no. 1008, 22 September 1995 (1995-09-22), pages 382-384, ISSN: 0028-8446.

D5: GHOSE K ET AL: 'An open pilot study of the preventive effect of nefopam in migraine headaches' HEADACHE QUARTERLY 1999 UNITED STATES, vol. 10, no. 3, 1999, pages 221-224, ISSN: 1059-7565.

D6: LASSETER K C ET AL: 'Nefopam HCl interaction study with eight other drugs' JOURNAL OF INTERNATIONAL MEDICAL RESEARCH 1976, vol. 4, no. 3, 1976, pages 195-201.

2. *Novelty* **(Art. 33(2) PCT)**

2.1 **D1** and **D2** disclose studies on the *effects* of combinations of nefopam with morphine versus morphine alone given to patients after surgery. Side effects, namely *nausea and vomiting*, were *reduced* in the group of patients receiving morphine plus nefopam while analgesia was superior, compared to the patients receiving morphine alone.

D1 and **D2** would thus **anticipate** the *novelty* of the subject-matter of claims 1-5 and

7.

2.2 **D3** as well involves clinical studies of *combinations of morphine* with nefopam or with diclofenac or with both. Furthermore, the patients received *metoclopramide*. Concerning the side effects, there appears to be no comparative data of patients only receiving morphine alone.
However, according to **D3**, *p. 302, left-hand col., paragraph 2*, the morphine-sparing effect of nefopam is known.

Accordingly, **D3** would be ***prejudicial*** to the novelty of claims 1-5 and 7-10.

2.3 The subject-matter of claims 6 and 11-13 would appear to be ***novel*** in view of the available prior art:
The subject-matter of claims 11-13 particularly refers to (+)-nefopam, thus establishing novelty vis-à-vis the available prior art documents.

3. *Inventive Step* **(Art. 33(3) PCT)**

3.1 The *problem* to be solved in the present application is the provision of a medicament for the treatment of nausea, blurred vision, dizziness and emesis.

The *solution* of the present application resides in the use of *nefopam* for the manufacture of a medicament for the above-mentioned conditions.

3.2 *Nausea and vomiting* are well-known side effects associated with nefopam (see **D4-D6**). However, in particular cases, nefopam reduces *nausea and vomiting* associated with other drugs, for instance morphine (see *'novelty'* and **D1** to **D3**).
It would appear that side effects of *nefopam* ***and*** *particular drugs* are changed respectively influenced when nefopam is administered *in combination with* other particular drugs.
This phenomenon would appear to be due to interactions of the drugs (see **D1** to **D3** and **D6**).

However, it would *not* be *obvious* from the prior art that *nefopam* is effective for the treatment of nausea, emesis, blurred vision and dizziness, wherein the condition is *induced by chemotherapy*.

An inventive step could therefore be **acknowledged** for the subject-matter of claims 6 and 12.

3.3 The subject-matter of claims 11 and 13 relates to the use of the particular enantiomer ***(+)***-nefopam. The use of the racemic nefopam in the claimed therapeutic applications is already known (see '*novelty*' and e.g. **D1** to **D3**).
It is general knowledge in the art that enantiomers have different activity. Thus, the use of a single enantiomer instead of the racemate in a therapeutic application which is already known in the art would not be considered inventive.

An ***inventive step*** could therefore ***not*** be ***acknowledged*** for the subject-matter of claims 11 and 13.

4. *Industrial Applicability* **(Art. 33(4) PCT)**

The requirements of industrial applicability would be fulfilled for the subject-matter of claims 1-10.

11. Use according to any preceding claim, wherein the nefopam is (+)-nefopam.

12. Use according to claim 11, wherein the condition is induced by chemotherapy.

13. Use according to claim 11, wherein the condition is post-operative emesis.